Positron Emission Tomography:
Tool to Facilitate Drug Development and to Study Pharmacokinetics

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Outline of Talk

1. PET has high sensitivity and specificity
2. PET used in therapeutic drug development
3. Pharmacokinetic modeling of plasma concentration and tissue uptake can measure receptor density
4. Study drug distribution: “peripheral” benzodiazepine receptor
5. Study drug metabolism: inhibit defluorination

Imaging of neuroreceptors by PET

Illustration of requirements for PET: Isotope production, radiochemistry to create ligand, positron camera for imaging.

Positron Emission Tomography

Title slide for a talk on this topic by Simon R. Cherry at the University of California-Davis.

CMGI

PET vs. MRI

Chart comparing PET with MRI

Radionuclide (11C): high sensitivity
Ligand (raclopride): high selectivity
Radioligand [11C]raclopride: high sensitivity & selectivity

PET provides greater sensitivity but less special resolution than MRI.

Radioligand = Drug + Radioactivity

1. Drug administered at tracer doses

a) No pharm effects
b) Labels <1% receptors
c) Labeled subset reflects entire population

2. Radioligand disposed like all drugs

a) Metabolism & distribution

3. Radiation exposure

NIH Rodent PET Camera
^{18}F bone uptake rat

PET scan image.

Developed By: Mike Green & Jurgen Seidel

PET: Tool in Therapeutic Drug Development

- Determine dose and dosing interval
- Identify homogeneous group
- Biomarker for drug efficacy
- Monitor gene or stem cell therapy

Lazabemide blocks [11C]deprenyl binding to monoamine-oxidase-B (MAO-B)

Images of baseline, 25 mg bid, 50 mg bid, and 36 hours later.

Selegilene is more potent and longer acting than lazabemide

Images at baseline, 5 mg bid, 1 week later and 3 weeks later.

PET: Tool in Therapeutic Drug Development

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Dopamine Transporter: Located on DA Terminals
Removes DA from Synapse

Illustration of this process et synapse.

SPECT Imaging of Dopamine Transporter
in Caudate and Putamen of Human Brain

MRI SPECT

Illustration of imaging differences in MRI vs. SPECT.

123I-β-CIT Dopamine Transporter SPECT: Decreased in Parkinson's Disease

Images of this activity in a healthy individual vs. a Parkinson Stage 1 patient.

PET: Tool in Therapeutic Drug Development

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Serial Dopamine Transporter Imaging in a Parkinson Patient

Images comparing baseline with 22 months, 34 months, and 46 months.

Institute for Neurodegenerative Disorders

PET Imaging of Amyloid:
Biomarker for Alzheimer's Disease

Images comparing AD to Control.

University of Pittsburgh
PET Amyloid Imaging Group

PET: Tool in Therapeutic Drug Development

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Gene Therapy Using Viral Vectors

Viral vectors deliver gene
that synthesizes dopamine (DA)
Infuse virus into striatum (target cells)
Target cells express the DA gene

Illustration of gene therapy.

PET Dopamine Imaging in
Hemi-Parkinson Monkey:
Monitors gene for DA synthesis in right striatum

. PET Imaging to Monitor Embryonic Stem Cell Treatment of “Parkinson Disease” in Rats

PET images of normal, unilateral lesions and embryonic stem cells in PET & MRI.

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Brain Uptake of [18F]Fluoxetine:
Measures Density of Serotonin Transporters &
Affinity of Fluoxetine

Illustration of brain drug in a patient compared with brain drug in a healthy subject over time.

Brain Uptake of [18F]Fluoxetine: Measures Density of Serotonin Transporters & Affinity of Fluoxetine

Illustration of brain drug in a patient compared to brain drug in a healthy subject over time.

Brain Uptake of [18F]Fluoxetine: Measures Density of Serotonin Transporters & Affinity of Fluoxetine

Illustration of a brain drug in a patient compared to brain drug in a healthy subject over time at different doses.

Brain Uptake of [18F]Fluoxetine: Measures Density of Serotonin Transporters & Affinity of Fluoxetine

Illustration of brain drug in patient compared to brain drug in a healthy subject over time. Doses normalized to body weight.

Brain Uptake of [18F]Fluoxetine: Measures Density of Serotonin Transporters & Affinity of Fluoxetine

Illustration of brain drug in patient compared to brain drug in a healthy subject over time. Doses normalized to body weight. Doses normalized to body weight.

Brain Uptake of [18F]Fluoxetine:
Measures Density of Serotonin Transporters

Illustration of brain drug in patient compared to brain drug in a healthy subject over time. Effects of liver disease.

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Binding Potential (BP)
BP equals uptake in brain relative to how much activity is delivered in arterial plasma

Chart illustrating the binding potential in the brain comparing drug in plasma with volume in brain.

Binding Potential: Independent of Injected Dose*

Double Plasma Input =>Double Brain Response

*If ligand does not saturate receptors - i.e. if tracer doses used

Charts illustrating this.

BP can be calculated from the Area Under Curve (math integral)
as well as rate constants (math differential).

From curves of plasma and brain radioactivity over time,
estimate rate constants of entry and removal to/from tissue

Formula for this calculation.

Tissue uptake is proportional to density of receptors and the affinity of the drug

Formula for binding potential.

SUMMARY PET KINETICS

-Organ uptake is proportional to receptor density and affinity of drug
-Binding Potential (BP) = density X affinity
-"Drug Exposure" to tissue is AUC of:
plasma concentration *vs.* time
-"Response" (uptake) of tissue is AUC of:
tissue concentration *vs.* time

-BP also equals ratio of rate constants of entry and removal to/from tissue

Major Point of PET Pharmacokinetics

(in words)

- Plasma pharmacokinetics provides a limited view of what's happening to drug in plasma.
- PET provides a limited view of what's happening to drug in tissue.
- Concurrent measurement of drug in plasma and of drug in tissue allows quantitation of the target of drug action
– *i.e.*, receptor.

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“Peripheral” Benzodiazepine Receptor

1. Mitochondrial protein highly expressed in macrophages and activated microglia
2. Exists in periphery and brain
3. Multiple potential functions: steroid synthesis, nucleotide transport
4. Distinct from typical benzodiazepine $GABA_A$ receptor in brain
5. Marker for cellular inflammation

Receptor Blockade [11C]PBR28 in Monkey Brain: more radioligand in plasma and brain

Chart illustrating this and comparing baseline with receptors blocked.

MONKEY WHOLE BODY SCANS [11C]PBR28
Receptor blockade displaces from lung & kidney
Drives more to metabolism (liver) and exretion (urine)

Whole body scans of monkey at baseline and after blockade.

Human with low uptake is similar to monkey with receptor blockade

Compares A) regular healthy subject with B) odd healthy subject.
Graphic illustration.

Some HEALTHY Subjects May have No Receptor Binding of [11C]PBR28

Images of organs that demonstrate this occurrence.

Nonbinders showed a trend of higher plasma [11C]PBR28

INFLAMMATION IMAGING
On-going Studies

Neurocysticercosis
Multiple sclerosis
HIV with cognitive impairment
Alzheimer's disease
Atherosclerosis

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[18F]FCWAY: Defluorination
Bone uptake: human skull at 2 h

Images that illustrate this.

Miconazole Inhibits Defluorination & Bone Uptake

Images of defluroination and bone uptake at various times.

Disulfiram: Decreases Skull Activity &
Increases Brain Uptake

Images of this at baseline and with Disulfiram.

Disulfiram: Decreases skull uptake of fluoride & Increases brain uptake of [18F]FCWAY

Charts comparing this uptake in the skull and the temporal cortex.

Disulfiram: Decreases plasma fluoride & Increases plasma radiotracer [18F]FCWAY

Charts that illustrate this activity.

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FDA Critical Path Initiative

- Approvals for new drugs declining
- R&D funding by industry and NIH is increasing
- Problem: tools are inadequate for efficient evaluation of new drugs in the “critical path” of development
- Still using old tools like liver enzymes and hematocrit to evaluate safety and efficacy
- Need new **Product Development Toolkit**

<u>CRITICAL PATH</u> to New Medical Products
FDA, March 2004

"There is currently an urgent need for additional **public-private collaborative work** on applying technologies such as … new imaging technologies.

Opportunity: **Imaging technologies**, such as molecular imaging tools in neuropsychiatric diseases or as measures of drug absorption and distribution, may provide powerful insights into the distribution, binding, and other biological effects of pharmaceuticals."

Copy of website for the Foundation for the NIH

http://www.fnih.org/

The website for the Biomarkers Consortium

Information for this initiative can be found at http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_101006/page3

Self-Assessment Quiz:
True or False?

- Positron emission tomography (PET) studies involve the injection of a radioactively labeled drug that emits a particle called a positron.
- PET shows the location of radioactivity in a cross section (or tomograph) of the body.
- PET can be used to quantify the density of specific proteins in the body.
- Compartmental modeling of PET data typically uses measurements over time of 1) PET images of the target tissue and 2) concentrations of unchanged parent radioligand in plasma.